Abstract

Background: Former American football players have higher prevalence of cognitive impairment than the US population. It remains unknown what aspects of playing football are associated with neuropsychiatric outcomes.

Hypothesis/Purpose: We hypothesized that seasons of professional football, playing position, and experience of concussions were associated with cognition-related quality of life (QOL) and indicators of depression and anxiety.

Study Design: Descriptive Epidemiology Study

Methods: We examined whether seasons of professional football, playing position, and experience of concussions, measured by self-report of 10 symptoms, were associated with cognition-related QOL and indicators of depression and anxiety in a cross-sectional survey, conducted 2015-2017. Cognition-related QOL was measured by the short form of the Quality of Life in Neurological Disorders, Applied Cognition. The Patient Health Questionnaire (PHQ)-4 measured depression and anxiety symptoms. Of 13,720 eligible men with apparently valid contact information, 3,506 players had returned a questionnaire at the time of this analysis (response rate=25.6%).

Results: Seasons of professional play (risk ratio (RR) per 5 seasons=1.19, 95% CI=1.06, 1.34) and playing position were associated with cognition-related QOL. Each 5 seasons of play was associated with 9% increased risk of indicators of depression at borderline statistical significance (p=0.05). Compared with former kickers, punters and quarterbacks, men who played any other position had higher risk of poor cognition-related QOL, depression and anxiety. Concussion symptoms were strongly associated with poor cognition-related QOL (highest concussion quartile, RR=22.2, p<0.0001), depression (highest quartile, RR=6.0, p<0.0001) and anxiety (highest quartile, RR=6.4, p<0.0001), even 20 years after last professional play.

Conclusion: Our data suggest that seasons of play and playing position in the NFL are associated with lasting neuropsychiatric health deficits. Additionally, poor cognition-related QOL, depression, and anxiety appear to be associated with concussion in the long term.

Key terms: Sports injuries (D001265); Post-concussion syndrome (D038223); Cognitive Function (D003071); Depression (D003863); Anxiety (D001007); Football (D005538).

What is known about the subject: Former American football players have higher prevalence of cognitive impairment than the general US population.

What this study adds to existing knowledge: Each season of professional play was associated with increased risk of poor cognition-related QOL. Compared with former kickers, punters and quarterbacks, men who played any other position had higher risk of

poor cognition-related QOL, depression and anxiety. Associations of concussion symptoms with cognition-related QOL, depression and anxiety remained even 20 years after last professional play.

INTRODUCTION

Cognitive impairment[11, 15], depression,[14, 16, 31, 32] and anxiety[30, 32, 35] are established acute sequelae of concussion. Recently, public attention has focused on the long-term health of former professional American-style football players as an occupational group exposed to an unusually high number of concussions and sub-concussive blows. Several studies have compared the prevalence of neurological disorders and cognitive function in former National Football League (NFL) players with the general population, finding far higher than expected prevalence of neurodegenerative disease mortality,[34] and cognitive impairment[18, 41, 50] Smaller studies using convenience samples have found deficits in neuropsychiatric function and brain abnormalities, as well as chronic traumatic encephalopathy in postmortem brains of former players.[4, 22, 36] Although studies have found similar prevalence of major depression in NFL players versus the general public,[43, 50] whether depression or anxiety are associated with seasons of NFL play or playing position is unknown. More generally, the extent to which depression and anxiety may be long-term sequelae of concussion is largely unknown[19, 25, 27], as concussion studies predominantly have <1 year of follow-up[8, 9, 14, 16, 17, 26, 30-32, 35, 46, 51].

Current findings suggest that playing in the NFL may cause increased risk for cognitive problems and neurodegenerative disease[4, 18, 34, 36, 41, 50], however, existing studies have several important limitations. Most studies do not account for factors that differ between NFL players and the general population. NFL players typically have participated extensively in youth and college sports, which carry risk of concussion and subconcussive blows[3, 7, 14, 20, 27, 37, 42, 48, 49]. These exposures prior to NFL play may account for some of the neuropsychiatric risk in former NFL players versus the general

population.[3, 47-49]. For example, two of three samples that included former NFL players reported that playing organized football before age 12 was associated with cognitive deficits and depression[3, 47-49]. Post-mortem brain studies provide evidence that former players with neuropsychiatric symptoms have physical abnormalities in brain structure. However, these studies suffer from potential selection bias, in that they are overwhelmingly comprised of men who had neuropsychiatric symptoms in life. Thus, the magnitude of risk and specific factors of NFL play associated with subsequent cognitive and mood problems remains unknown. Studies comparing former NFL players with one another in a sample not selected for neuropsychiatric symptoms could mitigate some of these methodological issues. A dose-response association of neuropsychiatric outcomes with seasons of NFL play would provide evidence for the hypothesis that professional football causes worse neuropsychiatric outcomes[15, 24]. A lack of such an association would be evidence against causation.

Studies of former NFL players have examined the association of self-reported concussions and cognitive impairment,[18] physician's diagnosis of Alzheimer's Disease[18], and depression,[19, 40] with varied findings. However, although a longitudinal validation study found that self-reported concussions had moderate reliability, their use as an exposure measure may be problematic. Players whose physical and mental health declined between surveys tended to report more concussions in the second survey compared with the first, suggesting that current health influenced report of past concussions.[28] Additionally, medical records of concussions have poor agreement with athlete recollections, due to nondisclosure or non-treatment.[29] Thus, seasons of play and playing position, which are associated with concussions[11, 38], may serve as less

biased, more reliably recalled exposure measures than direct reporting of concussion exposure.

In the present study we examined whether seasons of play and playing position in the NFL were associated with poor cognition-related quality of life (QOL), depression and anxiety in a large sample of former players, the Football Players Health Study (FPHS). We further examined whether self-reported concussion symptoms during playing years explained possible associations. As non-head injury and pain have been associated with cognitive function, depression, and anxiety,[6, 21, 45] we examined associations of our exposures further adjusted for these factors. We accounted for age at which organized football was first played in these analyses and examined the independent association of age at first football with the outcomes.

METHODS

Sample

Our study targeted former players who participated in the NFL since 1960, the year the transition to helmets with hard plastic shells was essentially complete. We obtained home or email addresses from the NFL Players Association for 14,906 players, of which 1,186 were returned as invalid. The remaining 13,720 players were mailed or emailed a questionnaire. At the time of this analysis, 3,506 players had responded. The study was approved by the Beth Israel Deaconess Medical Center Institutional Review Board.

Measures

Football exposures. Players were asked to indicate the positions they most often played professionally. Response options included: offensive line, defensive line, linebacker, defensive back, running back, wide receiver, tight end, quarterback, kicker/punter, and special teams. The reference category was kicker/punter. As nearly every player who played special teams also listed an offensive or defensive position, we created an additional variable to indicate participation in special teams, in three levels: none, “special-strength” for players who also played offensive, defensive line, or tight end, and “special-speed” for players who also played running back, wide receiver, defensive back, or linebacker. For 10 men who did not select a position, we identified their NFL playing position via internet search.

Players were asked, “How many seasons did you actively practice or play professional football?” Additionally, the first and last calendar year of professional play were queried. Seventy-five men were missing seasons of play. We obtained data for 53 men from the Pro Football Reference[1]. The remaining 22 men were excluded in analyses using this variable.

We queried 10 football-related concussion symptoms during playing years with, “While playing or practicing football, did you experience a blow to the head, neck, or upper body followed by: headaches, nausea, dizziness, loss of consciousness, memory problems, disorientation, confusion, seizure, visual problems, and feeling unsteady on your feet.” Response options for each symptom were: no, once, 2-5, 6-10, or 11+ times. We coded these as 0, 1, 3.5, 8 and 13 and calculated the mean across all 10 items. We divided this mean by seasons of professional play to create a mean concussion symptom score per season. Last, we calculated quartiles of the concussion score to

examine a possible dose-response between symptoms and neuropsychiatric outcomes. We additionally created three groups of playing positions based on mean concussion symptoms at the time of head impact per season averaged across all players in that position: 1) low: kickers, punters and quarterbacks; 2) medium: wide receivers, defensive backs, linemen, tight ends; and 3) high: running backs, line backers, and special teams.

Players were asked, “How old were you when you began to play organized football?” We dichotomized age at first play as <12 or ≥12 years, based on prior research[3, 48]. A small number of men (N=47) were missing age at first play and were excluded in analyses using this variable.

Cognition-related QOL. The short form of the Quality of Life in Neurological Disorders, Applied Cognition-General Concerns (Neuro-QOL) was used to assess cognition-related QOL.[12] Eight items queried past 7-day cognitive difficulties (e.g., “I had to read something several times to understand it”). Response options were: 0: never, 1: rarely (once), 2: sometimes (2-3 times), 3: often (once/day), or 4: very often (several times/day). Responses were summed to create a continuous measure. A US population sample (N=1,109) was used to create standardized T-scores with mean=50 and standard deviation (SD)=10[12]. Based on published guidelines, we created an indicator of “severe symptoms or impairment” using a score ≤30, which corresponds to ≤2 SD below the US population mean (approximately equivalent to the lowest 2.5% of the US population).[2] The short form had excellent internal consistency in our data (Cronbach alpha=0.97). Ten men did not respond to the Neuro-QOL questions and were excluded in these analyses.

Indicators of depression and anxiety. The Patient Health Questionnaire (PHQ)-4 assessed symptoms of depression and anxiety. The PHQ-4 queries 2 past-two-week depression symptoms (the PHQ-2: “Little interest or pleasure in doing things”; “Feeling down, depressed or hopeless”) and 2 anxiety symptoms (the Generalized Anxiety Disorder Scale (GAD)-2: “Feeling nervous, anxious or on edge”; “Not being able to stop or control worrying”). Response options included: 0:Not at all; 1:Several days; 2:More than half the days; and 3:Nearly every day. Responses were summed separately for depression and anxiety and dichotomized at ≥3 for each, indicating, respectively, high depressive symptoms or high anxiety symptoms. In a meta-analysis of 4 studies, a cutoff of 3 had sensitivity=0.76 and specificity=0.81[33, 39] Current use of medication for depression and anxiety (each coded yes/no) were queried separately. Men were considered to have indicators of depression if they met the PHQ-2 cutoff or were taking medications for depression. Men were considered to have indicators of anxiety if they met the GAD-2 cutoff or were taking medications for anxiety. Three men did not respond to the PHQ-4 and were excluded.

Pain medication and surgeries. Pain medication use was queried with, “During your active playing years did you take pain control medications once a week or more (not just for an acute injury)?” Response options included aspirin or tylenol, ibuprofen, and prescription medication use. As only prescription pain medication use was associated with our outcomes, we included only that variable in subsequent models. Experience of 7 types of surgeries during playing years was queried: anterior cruciate ligament (ACL) reconstruction, neck, back, knee, ankle, shoulder, and hand surgery. We created a count of the number of types of surgeries from these responses (e.g., a player

who had at least one neck, hand, and back surgery would have had 3 types of surgeries).

Demographic factors. Race was coded as: Black, White, or other races. Age at questionnaire was in years.

Statistical Analyses

To investigate potential participation bias, we compared FPHS responders to non-responders. Non-responders were men we attempted to contact who did not join the study. Data for 7,772 non-responders were obtained through linkage with the Pro Football Reference dataset (which includes only players with regular- or post-season statistics)[1]. We also compared the racial distribution of the FPHS to that of a prior stratified random sample of pension-eligible NFL retirees[50].

We ascertained the prevalence of poor cognition-related QOL, depression and anxiety by player position and number of professional seasons. Next, to determine the association of our outcomes with position and professional seasons we fit two models for each outcome: 1) position, seasons of professional play, age at questionnaire and race; and 2) further adjusted for concussion symptoms at the time of head impact. Additionally, as non-head injury and experience of pain have been associated with cognitive function, depression and anxiety[6, 21, 45], we fit a third model further adjusted for number of surgeries, as an indicator of non-head injury, and regular use of prescription pain medication during playing years. We also examined our outcomes in association with the three groups of playing positions.

As associations with seasons of play and position may differ by era of play, we divided players into 2 groups by the median first calendar year of play (1984) and tested

seasons-of-play-by-era and position-by-era interaction terms. We conducted sensitivity analyses further adjusted for age at first organized football and, to examine the influence of outliers, with seasons of play top-coded at the 95th percentile, such that >12 seasons were coded as 12 seasons.

We examined age at first organized football dichotomized at age 12 and as a continuous variable. We fit a model for each of these exposures for cognition-related QOL, depression and anxiety as the dependent variables adjusted for age at interview and race. Finally, as loss of consciousness may be more accurately recalled than other concussion symptoms and characterizes severe concussions,[5] we conducted analyses with loss of consciousness as the exposure in association with our three outcomes, adjusted for age and race.

We conducted sensitivity analyses using inverse probability weighting[44] to explore possibly effects of bias in study participation. We estimated probability of participation based on position, start year, end year, and seasons of play using Pro Football Reference data for non-responders. We fit models with participants weighted by the inverse of this probability. Statistical analyses were conducted in SAS (SAS Institute). We estimated risk ratios using generalized estimating equations (PROC GENMOD)[52].

RESULTS

Respondents had a mean age of 52.8 years (SD=14.2) and had last played professional football <1 to 55 years prior to the questionnaire (median=24 years, IQR=10-35 years, Table 1). In comparisons of responders and non-responders using the Pro Football Reference Dataset, responders played slightly more seasons of football

than non-responders (responders, median=6, interquartile range (IQR)=3 to 9; non-responders, median=5, IQR=2 to 8) and began their professional career earlier (responders, median=1984, IQR=1973 to 1997; non-responders, median=1990, IQR=1981 to 1999). The distribution of positions in the FPHS differed from that of non-responders, with offensive linemen comprising a larger percentage of our sample (FPHS: 20.9% versus non-responders: 14.9%), and defensive backs comprising a smaller percentage of our sample (14.7% versus 19.0%, p<0.001, Table 2). The racial distribution of the FPHS was similar to that of a prior stratified random sample of pension-eligible NFL retirees (FPHS: 59% white, 38% Black, 4% other races; random sample, weighted: 57% white, 41% Black, 2% other races)[50].

Table 1: Demographic factors, age at first play, concussion symptoms during playing years and neuropsychiatric outcomes by playing position and number of seasons played among former NFL players, Football Players Health Study, N=3,506

		Age, years	Number of professional seasons	Age first organized football	Mean concussion symptoms	Loss of conscious-ness	Race, white
	N	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	% (N)
Total	3506	52.8 (14.2)	6.8 (3.7)	11.8 (3.1)	3.2 (2.8)	1.6 (2.6)	58.6 (2053)
Seasons in the NFL							
1	137	48.9 (13.9)	1.0 (0.1)	11.3 (3.2)	2.5 (2.4)	1.2 (2.3)	69.3 (95)
2-4	977	49.6 (14.4)	3.1 (0.8)	11.5 (3.2)	2.9 (2.6)	1.4 (2.3)	59.4 (580)
5-6	707	52.3 (14.7)	5.4 (0.5)	11.7 (3.1)	3.1 (2.7)	1.6 (2.5)	55.9 (395)
7-9	817	54.7 (13.8)	7.9 (0.8)	11.8 (3.0)	3.4 (2.8)	1.8 (2.8)	56.2 (459)
≥10	846	55.9 (12.8)	12.0 (2.1)	12.2 (3.1)	3.4 (3.0)	1.9 (2.7)	60.9 (515)
Position							
Kicker/punter	107	51.9 (12.5)	8.8 (5.4)	13.7 (3.7)	1.3 (1.7)	0.6 (1.1)	91.6 (98)
Quarterback	152	55.2 (13.3)	9.0 (4.7)	11.4 (3.0)	2.0 (1.6)	1.3 (1.5)	91.4 (139)
Wide receiver	331	51.6 (14.3)	6.5 (3.7)	11.5 (3.2)	2.7 (2.5)	1.8 (2.5)	42.6 (141)
Tight end	255	50.7 (14.9)	6.7 (3.6)	11.7 (3.0)	3.1 (2.6)	1.6 (2.6)	71.8 (183)
Running back	379	55.4 (13.9)	5.8 (3.1)	11.5 (3.0)	3.5 (2.9)	1.8 (2.7)	38.0 (144)
Offensive line	749	51.7 (14.3)	7.0 (3.9)	12.1 (2.9)	3.2 (2.7)	1.2 (2.3)	80.9 (606)
Line backer	571	52.7 (13.8)	6.5 (3.4)	11.4 (3.0)	3.7 (3.0)	2.0 (2.9)	59.5 (340)
Defensive back	526	53.2 (14.3)	6.4 (3.2)	11.2 (3.1)	3.1 (2.7)	2.0 (2.8)	31.9 (168)
Defensive line	436	53.6 (14.4)	6.9 (3.6)	12.5 (3.2)	3.4 (3.1)	1.6 (2.8)	53.7 (234)
Special teams							
Did not play often	2598	52.5 (14.1)	7.0 (3.9)	11.9 (3.2)	3.1 (2.8)	1.5 (2.5)	60.5 (1572)
Strength	216	54.6 (14.7)	6.5 (3.7)	12.0 (2.7)	3.5 (2.8)	1.9 (3.1)	74.1 (160)
Speed	692	53.3 (14.2)	6.2 (3.1)	11.3 (3.0)	3.4 (2.7)	2.0 (2.7)	46.4 (321)

Table 2. Distribution of playing positions in the Football Players Health Study (FPHS) and among non-responders

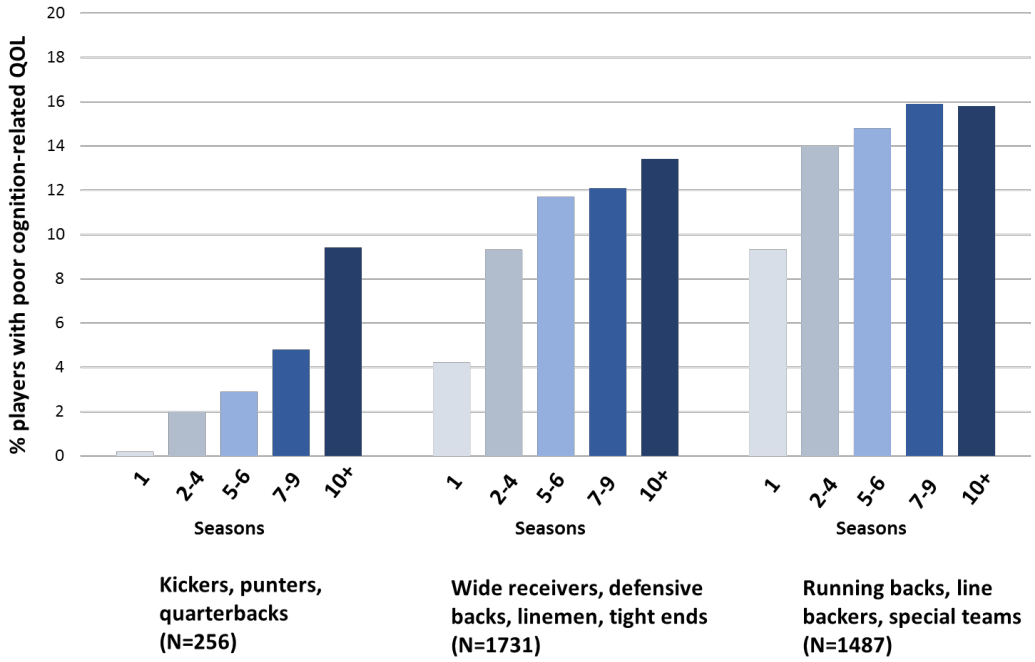
	FPHS (N=3,506)†		Non-responders (N=7,772)	
Position*	**N†**	**%**	**N**	**%**
Kicker	192	4.9	220	2.8
Quarterback	169	4.4	304	3.9
Wide receiver	375	9.7	1009	13.0
Tight end	291	7.5	478	6.2
Running back	379	9.8	970	12.5
Line backer	581	15.0	1063	13.7
Defensive back	573	14.7	1479	19.0
Defensive line	504	13.0	1098	14.1
Offensive line	812	20.9	1151	14.8

†Data for non-responders was obtained through linkage with the Palmer-Pullis Pro Football Dataset. Ns per position sum to more than the total in the FPHS because players were permitted to endorse more than one position. For non-responders, each player was assigned only one position.

*Chi-square p<0.001

One in eight respondents reported poor cognition-related QOL (12.4%) with T-scores ≤30, indicating severe impairment. Prevalence of poor cognition-related QOL was similar among players younger than 55 years (severe impairment, 13.3%, N=248 of 1861). Cognition-related QOL was associated with seasons of professional play and playing position (Figure). Of men who played only 1 season, 5.8% had poor cognition-related QOL versus 12.6% of men with >1 season (p<0.05).

Figure. Poor cognition-related quality of life by number of professional seasons and playing position among former National Football League players, Football Players Health Study (N=3,474)†



†Poor cognition-related quality of life was defined as a Neuro-QOL score ≤2 standard deviations below the US population mean (T-score≤30). Positions were grouped according to the mean concussion symptoms per season for each position averaged across all players in that position: low (≤2 symptoms/season: kickers, punters and quarterbacks); medium (>2 to 3.3 symptoms/season: wide receivers, defensive backs, linemen, tight ends); high (>3.3 symptoms/season: running backs, line backers, special teams).

Seasons of professional play (RR per 5 seasons=1.19, 95% CI=1.06, 1.34, p<0.01) and playing position were associated with cognition-related QOL in models adjusted for age and race (Table 3, Model 1). Compared to kickers/punters, running backs, defensive linemen, and line backers were at elevated risk of poor cognition-related QOL.

Table 3. Risk of poor cognition-related quality of life in association with number of professional seasons and playing position, Football Players Health Study, N=3,474†

		Poor cognition-related quality of life		
		Model 1: Adjusted for age at questionnaire and race	**Model 2: Model 1, further adjusted for concussion symptoms during playing years**	**Model 3: Model 2, further adjusted for pain medication and surgeries during playing years**
	N	**Risk ratio (95% confidence interval)**		
NFL seasons (per 5 seasons)		1.19 (1.06, 1.34)**	1.00 (0.89, 1.13)	0.97 (0.86, 1.10)
Position				
Kicker/punter	107	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]
Quarterback	151	1.42 (0.50, 4.00)	0.95 (0.35, 2.63)	0.99 (0.36, 2.71)
Wide receiver	328	2.06 (0.82, 5.14)	0.95 (0.39, 2.36)	1.03 (0.42, 2.54)
Tight end	252	1.60 (0.61, 4.18)	0.71 (0.27, 1.84)	0.74 (0.29, 1.92)
Running back	376	3.64 (1.49, 8.90)**	1.31 (0.54, 3.19)	1.39 (0.58, 3.38)
Offensive line	747	2.31 (0.96, 5.56)	0.98 (0.41, 2.36)	1.00 (0.42, 2.28)
Line backer	566	2.84 (1.17, 6.86)*	1.00 (0.42, 2.42)	1.06 (0.44, 2.54)
Defensive back	523	1.87 (0.76, 4.61)	0.79 (0.33, 1.93)	0.87 (0.36, 2.12)
Defensive line	434	2.71 (1.11, 6.60)*	1.07 (0.45, 2.57)	1.13 (0.46, 2.67)
Special teams				
Did not play often	2583	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]
Strength	215	1.21 (0.82, 1.79)	1.05 (0.74, 1.49)	1.05 (0.76, 1.49)
Speed	686	1.05 (0.84, 1.33)	1.00 (0.80, 1.24)	0.99 (0.80, 1.24)
Concussion symptoms during playing years				
Quartile 1	832		1.0 [Reference]	1.0 [Reference]
Quartile 2	900		3.44 (1.83, 6.48)***	3.25 (1.73, 6.12)***
Quartile 3	873		8.04 (4.45, 14.52)***	7.23 (4.01, 13.06)***
Quartile 4	879		22.25 (12.54, 39.48)***	18.89 (10.63, 33.57)***

Approximately one-quarter of respondents reported indicators of anxiety (25.9%) and depression (23.9%), and 18.3% of men reported both. Each 5 seasons of

professional play was associated with a 9% increased risk of having indicators of depression, at borderline statistical significance (RR=1.09, 95% CI=1.00, 1.18, p=0.05, Table 4, Model 1a). Depression and anxiety were associated with playing position, with running backs and defensive linemen at higher risk compared with kickers/punters. Risk of anxiety was not associated with seasons of professional play (Table 4, Model 1b).

Table 4. Risk of indicators of depression and anxiety in association with number of professional seasons and playing position, Football Players Health Study, N=3,484†

	Indicators of depression			Indicators of anxiety		
	Model 1a: Adjusted for age at questionnaire and race	**Model 2a: Model 1a, further adjusted for concussion symptoms during playing years**	**Model 3a: Model 2a, further adjusted for pain medication and surgeries during playing years**	**Model 1b: Adjusted for age at questionnaire and race**	**Model 2b: Model 1b, further adjusted for concussion symptoms during playing years**	**Model 3b: Model 2b, further adjusted for pain medication and surgeries during playing years**
	Risk ratio (95% confidence interval)			**Risk ratio (95% confidence interval)**		
NFL seasons (per 5 seasons)	1.09 (1.00, 1.18)	0.98 (0.90, 1.06)	0.95 (0.87, 1.03)	1.04 (0.96, 1.13)	0.93 (0.86, 1.01)	0.90 (0.84, 0.97)
Position						
Kicker/punter	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]
Quarterback	1.21 (0.66, 2.22)	0.93 (0.51, 1.70)	0.92 (0.50, 1.69)	0.97 (0.56, 1.69)	0.74 (0.43, 1.28)	0.74 (0.43, 1.28)
Wide receiver	1.19 (0.69, 2.05)	0.76 (0.45, 1.30)	0.77 (0.46, 1.38)	1.28 (0.80, 2.05)	0.81 (0.51, 1.27)	0.82 (0.52, 1.31)
Tight end	1.28 (0.74, 2.24)	0.80 (0.46, 1.38)	0.79 (0.46, 1.38)	0.93 (0.56, 1.54)	0.56 (0.34, 0.92)**	0.56 (0.34, 0.92)*
Running back	2.07 (1.23, 3.49)**	1.13 (0.67, 1.89)	1.13 (0.67, 1.90)	1.82 (1.15, 2.89)*	0.96 (0.61, 1.51)	0.96 (0.61, 1.51)
Offensive line	1.68 (1.01, 2.79)	1.01 (0.61, 1.67)	0.98 (0.58, 1.63)	1.47 (0.95, 2.27)	0.85 (0.55, 1.31)	0.82 (0.53, 1.28)
Line backer	1.50 (0.90, 2.52)	0.81 (0.48, 1.36)	0.81 (0.48, 1.36)	1.28 (0.82, 2.01)	0.66 (0.43, 1.04)*	0.66 (0.42, 1.04)
Defensive back	1.36 (0.81, 2.30)	0.82 (0.49, 1.37)	0.84 (0.50, 1.43)	1.26 (0.80, 1.99)	0.73 (0.47, 1.15)	0.76 (0.48, 1.20)
Defensive line	1.91 (1.14, 3.19)*	1.11 (0.67, 1.85)	1.10 (0.65, 1.84)	1.57 (1.00, 2.45)*	0.88 (0.57, 1.37)	0.87 (0.55, 1.35)
Special teams						
Did not play often	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]
Strength	1.08 (0.84, 1.39)	0.98 (0.78, 1.24)	0.98 (0.78, 1.24)	1.20 (0.95, 1.51)	1.08 (0.88, 1.34)	1.09 (0.89, 1.34)
Speed	0.97 (0.82, 1.14)	0.92 (0.79, 1.08)	0.92 (0.79, 1.07)	0.97 (0.83, 1.14)	0.99 (0.99, 1.00)	0.93 (0.80, 1.07)
Concussion symptoms during playing years						
Quartile 1		1.0 [Reference]	1.0 [Reference]		1.0 [Reference]	1.0 [Reference]
Quartile 2		2.22 (1.67, 2.94)***	2.12 (1.60, 2.82)***		2.17 (1.65, 2.86)***	2.08 (1.58, 2.75)***
Quartile 3		3.70 (2.85, 4.82)***	3.42 (2.63, 4.46)***		3.80 (2.94, 4.90)***	3.51 (2.72, 4.54)***
Quartile 4		6.01 (4.67, 8.74)***	5.31 (4.10, 6.87)***		6.41 (5.02, 8.19)***	5.65 (4.40, 7.26)***

Men were considered to have indicators of depression if they had a score ≥3 on the Patient Health Questionnaire (PHQ)-2 or current antidepressant use. Men were considered to have indicators of anxiety if they had a score ≥3 on the Generalized Anxiety Disorder Scale (GAD)-2 or current anti-anxiety medication use.

*p<0.05, **p<0.01, ***p<0.001

In analyses examining groups of positions, players in positions with medium or high mean concussion symptoms were at elevated risk of poor neuro-QOL, depression, and anxiety, compared with players in positions with low mean concussion symptoms (Table 5, Models 1a,b,c).

Interaction terms for era of play with seasons of play and position were not statistically significant. Results were similar in models adjusted for age at first football, continuously or dichotomized at <12 years, and in models with seasons of play top-coded.

Concussion symptoms at the time of football head impact were very strongly associated with subsequent cognition-related QOL, depression and anxiety. All players above the lowest 25% of concussion symptoms were at substantially higher risk of all three outcomes compared with players in the lowest 25%. The highest quartile of concussion symptoms was associated with 22.3-fold greater risk of poor cognition-related QOL, 6.0-fold greater risk of depression, and 6.4-fold greater risk of anxiety (all $p<0.001$). Adjustment for concussion symptoms attenuated associations of seasons of professional play and playing position with cognition-related QOL, depression and anxiety (Table 3, Model 2; Table 4, Models 2a, 2b). Further adjustment for use of prescription pain medication and number of surgeries during playing years somewhat attenuated associations of concussion symptoms with all three outcomes, although associations remained very strong (Table 3, Model 3; Table 4, Models 3a, 3b).

In models examining the three outcomes in association with position group, further adjustment for concussion symptoms fully attenuated all associations (Table 5, Models 2a,b,c).

Table 5: Association of position group with cognition-related quality of life and indicators of depression and anxiety

	Poor cognition-related QOL		Indicators of Depression		Indicators of Anxiety	
	Model 1a: Adjusted for seasons in NFL, age at questionnaire, and race	**Model 2a: Model 1a, further adjusted for concussion symptoms during playing years**	**Model 1b: Adjusted for seasons in NFL, age at questionnaire, and race**	**Model 2b: Model 1a, further adjusted for concussion symptoms during playing years**	**Model 1c: Adjusted for seasons in NFL, age at questionnaire, and race**	**Model 2c: Model 1c, further adjusted for concussion symptoms during playing years**
Position						
Low concussion risk†	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]
Medium concussion risk	1.72 (1.03, 2.88)*	0.93 (0.57, 1.52)	1.39 (1.02, 1.89)*	1.00 (0.75, 1.36)	1.39 (1.03, 1.86)*	0.96 (0.73, 1.27)
High concussion risk	2.23 (1.33, 3.73)**	1.03 (0.62, 1.68)	1.41 (1.03, 1.94)*	0.94 (0.70, 1.27)	1.45 (1.08, 1.95)*	0.92 (0.69, 1.22)

†Positions were grouped according to the mean concussion symptoms per season for each position averaged across all players in that position: low (≤2 symptoms/season: kickers, punters and quarterbacks); medium (>2 to 3.4 symptoms/season: wide receivers, defensive backs, linemen, tight ends); high (>3.4 symptoms/season: running backs, line backers, special teams).

*p<0.05, **p<0.01, ***p<0.001

Loss of consciousness strongly predicted each outcome; each increase in loss of consciousness was associated with a greater prevalence of poor health (Table 6, Analysis 1). Men who lost consciousness even once had substantially increased risk of all three outcomes compared with men who had never lost consciousness. To further explore our findings, we conducted two additional analyses. First, we restricted our sample to men who had last played professional football 20 or more years prior to the questionnaire (N=1,863). In this subsample, loss of consciousness remained strongly associated with cognition-related QOL, depression and anxiety (Table 6, Analysis 2). Second, to examine the effects of concussion without loss of consciousness, we restricted to men who had never lost consciousness. Estimates were very similar in this subsample compared to the whole sample (highest concussion quartile: 25.0-fold greater risk of poor cognition-related QOL, 5.9-fold greater risk of depression, and 6.1-fold greater risk of anxiety, all $p<0.0001$).

Age at first organized football was not associated with cognition-related QOL, depression or anxiety, whether continuously or dichotomized at <12 years (poor neuro-QOL, age <12 RR=1.05, 95% CI=0.88, 1.26; depression, RR=1.00, 95% CI=0.89, 1.13; anxiety, RR=1.04, 95% CI=0.93, 1.17, all $p>0.05$). In analyses exploring potential effects of participation bias, results were nearly identical in models weighted and not weighted for the inverse probability of participation.

Table 6: Loss of consciousness during football in association with cognition-related quality of life and indicators of depression and anxiety, Football Players Health Study, N=3,394†

		Poor cognition-related quality of life	Indicators of depression	Indicators of anxiety
	N	**Risk ratio (95% CI)**	**Risk ratio (95% CI)**	**Risk ratio (95% CI)**
Analysis 1: Entire cohort				
Loss of consciousness during playing years				
Never	1631	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]
Once	760	1.67 (1.28, 2.18)***	1.39 (1.17, 1.65)***	1.26 (1.07, 1.48)**
2-5 times	810	2.54 (2.01, 3.21)***	2.08 (1.79, 2.40)***	1.87 (1.63, 2.15)***
6-10 times	110	4.87 (3.52, 6.72)***	3.28 (2.68, 4.03)***	2.71 (2.20, 3.33)***
≥11 times	83	6.15 (4.60, 8.21)***	3.59 (2.95, 4.36)***	3.39 (2.84, 4.05)***
Analysis 2: Men who last played football ≥20 years prior (N=1,863)				
Loss of consciousness during playing years				
Never	800	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]
Once	440	1.41 (0.96, 2.06)	1.38 (1.08, 1.76)*	1.29 (1.02, 1.64)*
2-5 times	519	2.28 (1.65, 3.14)***	2.02 (1.64, 2.49)***	1.84 (1.50, 2.25)***
6-10 times	63	5.65 (3.71, 8.63)***	3.43 (2.52, 4.68)***	2.73 (1.95, 3.81)***
≥11 times	41	4.91 (3.10, 7.78)***	3.69 (2.72, 5.02)***	3.79 (2.91, 4.94)***

**p<0.01, ***p<0.001

†All models adjusted for age at questionnaire and race. Poor cognition-related quality of life was defined as a Neuro-QOL score ≤2 standard deviations below the US population mean. Men were considered to have indicators of depression if they had a score ≥3 on the Patient Health Questionnaire (PHQ)-2 or current antidepressant use. Men were considered to have indicators of anxiety if they had a score ≥3 on the Generalized Anxiety Disorder Scale (GAD)-2 or current anti-anxiety medication use.

DISCUSSION

We found each 5 seasons of professional play was associated with 19% greater risk of poor cognition-related QOL. Among men who played only 1 season in the NFL, 35.8% had poor cognition-related QOL versus 12.7% in men with >1 season, again suggesting that professional play placed players at increased risk, over and above risk resulting from college and youth football. Regarding individual positions, running backs and defensive linemen were at elevated risk of all three outcomes we examined, compared with kickers and punters. In addition, we found that players in positions with medium or high mean concussion symptoms per season had greater risk of all three outcomes compared with players in low-mean-concussion-symptom positions (i.e., kickers, punters, and quarterbacks). Concussion symptoms at the time of head impact accounted for differences in cognition-related QOL and depression by playing seasons and by position, both individually and grouped, suggesting that experience of concussions underlies much of the association of NFL seasons and playing position with the outcomes.

Concussion symptoms and loss of consciousness were strongly associated with indicators of anxiety and depression, even decades after the injury. To our knowledge, only three large- or moderate-sized studies have examined depression[19, 25, 27] and no studies have examined anxiety symptoms in association with concussion at long time periods post-injury. Existing studies have typically examined symptoms within 1 year of injury,[26, 46] have lacked non-concussed comparison groups,[26, 32] or have unknown time between injury and psychiatric symptoms, with few exceptions[17]. Our results suggest anxiety and depression may be important long-term sequela of concussion.

Age at which organized football was first played was not associated with cognition-related QOL, depression or anxiety. Prior studies found associations of cognitive impairment and corpus callosum microstructure with young age at first organized football, but these were small- or moderate-sized convenience samples (N≤42[48, 49], N=214[3]). However, compared to typical youth sports participants, former professional athletes are likely to have played youth sports with unusual intensity (e.g., playing as a starter, having more game time, playing more seasons of sports across childhood) and hence may not be representative. In addition, for professional athletes, the effects of youth sports could be overpowered by subsequent professional exposures, and children more affected by injury would likely not continue to professional competition, possibly creating bias. Thus, former professional athletes are not ideal for the study of effects of youth sports.

Our study has important limitations. First, although the Neuro-QOL is a validated measure of cognition-related QOL,[12] given recent public attention regarding the association of concussion with later-life cognitive function, it is possible that players who experienced concussions are sensitized to possible cognitive symptoms and may over-report them, although this would not affect associations of cognitive function with seasons or position of play. Second, our football measures were of events that for some men occurred many years ago. Therefore, they are subject to recall bias. In particular, concussion symptoms may be difficult to accurately recollect. However, we also queried loss of consciousness events, which may be easier to recollect, and had similar findings. Third, we were unable to consider possible effects of subconcussive blows, which may be associated with cognitive function, though findings are mixed[10]. Fourth,

386estimates of the association between seasons of play and neuropsychiatric outcomes
387are likely biased by the healthy worker effect.[13] Players who remain in the NFL for many
388years are often those who have not been seriously injured[50]. This situation would bias
389effect estimates towards the null hypothesis; that is, our findings would be
390underestimates of true associations between seasons of play and health outcomes.
391Players may also have chosen or been unable to participate due to ill health or death
392from football-related exposures, which would reduce prevalence estimates.[34] Fifth, our
393questionnaire response rate was modest and could have been affected by participation
394bias. In fact, in comparisons with data from the Pro Football Reference, participants in
395the FPHS played more seasons, began their career earlier, and were more likley to be
396offensive linemen. However, participation bias could not account for our findings unless
397it was jointly related to both exposure and outcome[23]. Additionally, results were very
398similar in analyses weighted for the probability of participation.

399 Concussion history and life in football appear to be associated with cognitive and
400mental health complaints. Further efforts to reduce risk are warranted, and an enhanced
401mechanistic understanding of risks and ways to mitigate risk is needed. Active players,
402along with medical professionals who care for them, might consider their future health in
403deciding whether to continue a football career following concussion.
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